This listing of claims will replace all prior versions, and listings, of claims in the application:

Listing of Claims:

1. **(Currently Amended)** An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, and a targeting moiety that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein

said adzyme is resistant to cleavage by the catalytic domain,

said targeting moiety and said catalytic domain are heterologous with respect to each other,

said targeting moiety, when provided separately, binds to the substrate,

said catalytic domain, when provided separately, catalyzes the chemical reaction converting said substrate to one or more products, and

said adzyme has one or more properties, with respect to the reaction with said substrate, of (a) a potency at least 2 times greater than the catalytic domain or the targeting moiety alone; (b) a k_{on} of 10^3 $M^{-1}s^{-1}$ or greater; (c) a k_{cat} of 0.1 sec^{-1} or greater; (d) a K_D that is at least 5 fold less than the K_m of the catalytic domain; (e) a k_{off} of 10^{-4} sec^{-1} or greater, (f) a catalytic efficiency at least 5 fold greater than the catalytic efficiency of the catalytic domain alone, (g) a K_m at least 5 fold less than the K_m of the catalytic domain alone, and/or (h) an effective substrate concentration that is at least 5 fold greater than the actual substrate concentration.

2-3. **(Canceled)**

4. **(Original)** An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that catalyzes a chemical reaction converting said substrate to one or more products, and a targeting moiety that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein one or more of said products is an antagonist of an activity of said substrate.

5. **(Currently Amended)** An adzyme for enzymatically altering a substrate, the adzyme comprising: a catalytic domain that cleaves at least one peptide bond of said substrate to

produce one or more products, and a polypeptide targeting domain that reversibly binds with an address site on said substrate or with an address site on a second molecule that occurs in functional proximity to the substrate, wherein

said ~~chimeric protein construct~~ adzyme is resistant to cleavage by the catalytic domain,

said targeting domain ~~moiety~~, when provided separately, binds to the substrate,

said catalytic domain, when provided separately, cleaves at least one peptide bond of said substrate to produce one or more products, and

said adzyme is more potent than said catalytic domain or targeting moiety with respect to the reaction with said substrate.

6. **(Canceled)**

7. **(Currently Amended)** The adzyme of claim [[1]] 5, wherein the substrate is endogenous to a human patient.

8. **(Currently Amended)** The adzyme of claim 7, wherein ~~the effect of~~ the adzyme ~~on the substrate~~ is effective against the substrate ~~target molecule~~ in the presence of physiological levels of ~~an abundant~~ human serum protein.

9. **(Currently Amended)** The adzyme of claim 8, wherein the ~~abundant~~ human serum protein is human serum albumin.

10. **(Currently Amended)** The adzyme of claim [[2]] 5, wherein said adzyme has one or more properties, with respect to the reaction with said substrate, of (a) a potency at least 2 times greater than the catalytic domain or the targeting domain ~~moiety~~ alone; (b) a k_{on} of $10^3\ M^{-1}s^{-1}$ or greater; (c) a k_{cat} of 0.1 sec^{-1} or greater; (d) a K_D that is at least 5 fold less than the K_m of the catalytic domain; (e) a k_{off} of 10^{-4} sec^{-1} or greater, (f) a catalytic efficiency at least 5 fold greater than the catalytic efficiency of the catalytic domain alone, (g) a K_m at least 5 fold less than the K_m of the catalytic domain alone, and/or (h) an effective substrate concentration that is at least 5 fold greater than the actual substrate concentration.

11. **(Currently Amended)** The adzyme of claim 10, wherein the potency of the adzyme is at least 5 times greater than the catalytic domain or the targeting domain ~~moiety~~ alone.

12. **(Original)** The adzyme of claim 10, wherein the k_{on} is $10^6\ M^{-1}s^{-1}$ or greater.

13. (**Original**) The adzyme of claim 10, wherein the k_{cat} is 10 sec^{-1} or greater.

14. (**Original**) The adzyme of claim 10, wherein the K_D is at least 50 fold lower than the K_m of the catalytic domain.

15. (**Original**) The adzyme of claim 10, wherein the k_{off} is 10^{-3} s^{-1} or greater.

16. (**Original**) The adzyme of claim 10, wherein the catalytic efficiency is at least 20 fold greater than that of the catalytic domain alone.

17. (**Original**) The adzyme of claim 10, wherein the K_m is at least 20 fold less than that of the catalytic domain alone.

18-24. (**Canceled**)

25. (**Currently Amended**) The adzyme of claim [[1]] 5, wherein said adzyme is a fusion protein.

26. (**Currently Amended**) The adzyme of claim 25, wherein said fusion protein includes a linker between said catalytic domain and said targeting domain ~~moiety~~.

27. (**Currently Amended**) The adzyme of claim [[25]] 26, wherein said linker is an unstructured peptide.

28. (**Canceled**)

29. (**Original**) The adzyme of claim 27, wherein said linker includes one or more repeats of Ser_4Gly or $SerGly_4$.

30. (**Canceled**)

31. (**Currently Amended**) The adzyme of claim [[25]] 26, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting domain ~~moiety~~ such that said adzyme is more potent than said catalytic domain or targeting domain ~~moiety~~ with respect to the reaction with said substrate.

32. (**Canceled**)

33. (**Currently Amended**) The adzyme of claim [[25]] 26, wherein said linker is selected to provide steric geometry between said catalytic domain and said targeting domain ~~moiety~~ such that said targeting domain ~~address moiety~~ presents the substrate to the catalytic

domain ~~enzymatic domain~~ at an effective concentration at least 5 fold greater than would be present in the absence of the targeting domain ~~address moiety~~.

34. **(Canceled)**

35. **(Original)** The adzyme of claim 25, wherein the fusion protein is a cotranslational fusion protein encoded by a recombinant nucleic acid.

36. **(Canceled)**

37. **(Currently Amended)** The adzyme of claim [[1]] 5, wherein the substrate is a biomolecule produced by a cell.

38. **(Currently Amended)** The adzyme of claim [[1]] 5, wherein said substrate is a polypeptide.

39. **(Withdrawn)** The adzyme of claim 1, wherein the substrate is a polysacccaride, a nucleic acid, a lipid, or a small molecule.

40. **(Currently Amended)** The adzyme of claim [[1]] 38, wherein the substrate is a diffusible extracellular molecule.

41. **(Original)** The adzyme of claim 40, wherein the diffusible extracellular molecule is an extracellular signaling molecule.

42. **(Original)** The adzyme of claim 41, wherein the extracellular signaling molecule is an extracellular polypeptide signaling molecule.

43. **(Original)** The adzyme of claim 40, wherein the extracellular signaling molecule is selected from among: interleukin-1 and TNF-alpha.

44. **(Original)** The adzyme of claim 41, wherein the extracellular signaling molecule binds to a cell surface receptor and triggers receptor-mediated cellular signaling.

45. **(Withdrawn, Currently Amended)** The adzyme of claim [[1]] 38, wherein said substrate is a receptor.

46. **(Withdrawn)** The adzyme of claim 45, wherein said substrate is a unique receptor subunit of a heteromeric receptor complex.

47. **(Withdrawn)** The adzyme of claim 37, wherein the biomolecule is a component of a biomolecular accretion.

48. (**Withdrawn**) The adzyme of claim 47, wherein the biomolecular accretion is selected from among: an amyloid deposit and an atherosclerotic plaque.

49. (**Withdrawn**) The adzyme of claim 37, wherein the biomolecule is a biomolecule produced by a pathogen.

50. (**Withdrawn**) The adzyme of claim 49, wherein the pathogen is selected from among, a protozoan, a fungus, a bacterium and a virus.

51. (**Withdrawn**) The adzyme of claim 37, wherein the biomolecule is a prion protein.

52. (**Currently Amended**) The adzyme of claim [[1]] 5, wherein said substrate comprises a polypeptide and wherein said catalytic domain is a protease that cleaves at least one peptide bond of the substrate.

53-55. (**Canceled**)

56. (**Withdrawn**) The adzyme of claim 52, wherein said protease is a zymogen.

57. (**Canceled**)

58. (**Original**) The adzyme of claim 52, wherein said adzyme is purified from a cell culture in the presence of a reversible protease inhibitor.

59-60. (**Canceled**)

61. (**Withdrawn, Currently Amended**) The adzyme of claim [[1]] 5, wherein said substrate includes a chiral atom, and said catalytic domain alters the ratio of stereoisomers.

62. (**Withdrawn**) The adzyme of claim 38, wherein said catalytic domain alters the level of post-translational modification of the polypeptide substrate.

63. (**Canceled**)

64. (**Withdrawn**) The adzyme of claim 62, wherein the post-translation modification is selected from the group consisting of glycosylation, phosphorylation, sulfation, fatty acid modification, alkylation, prenylation and acylation.

65. (**Canceled**)

66. (**Currently Amended**) The adzyme of claim [[1]] 5, wherein the catalytic domain is selected from the group consisting of: a protease, an esterase, an amidase, a lactamase, a cellulase, an oxidase, an oxidoreductase, a reductase, a transferase, a hydrolase, an

isomerase, a ligase, a lipase, a phospholipase, a phosphatase, a kinase, a sulfatase, a lysozyme, a glycosidase, a nuclease, an aldolase, a ketolase, a Iyase, a cyclase, a reverse transcriptase, a hyaluronidase, an amylase, a cerebrosidase and a chitinase.

67-68. **(Canceled)**

69. **(Currently Amended)** The adzyme of claim [[68]] 5, wherein the adzyme is resistant to cleavage by the catalytic domain ~~autocatalysis~~ at an adzyme concentration that is about equal to the concentration of adzyme in a solution to be administered to a subject.

70. **(Original)** The adzyme of claim 37, wherein said adzyme alters the half-life of the biomolecule *in vivo*.

71. **(Canceled)**

72. **(Original)** The adzyme of claim 37, wherein said adzyme alters the distribution of the biomolecule *in vivo*.

73. **(Canceled)**

74. **(Original)** The adzyme of claim 37, wherein said adzyme reduces a biological activity of said biomolecule.

75. **(Canceled)**

76. **(Original)** The adzyme of claim 37, wherein said biomolecule binds a plurality of different molecules *in vivo*, and said adzyme alters the binding specificity of said biomolecule.

77. **(Canceled)**

78. **(Original)** The adzyme of claim 37, wherein said adzyme alters the interaction of said biomolecule with other molecules *in vivo*.

79. **(Canceled)**

80. **(Original)** The adzyme of claim 78, which alters one or more of: a receptor-ligand interaction, a protein-protein interaction and a DNA-protein interaction.

81. **(Canceled)**

82. **(Original)** The adzyme of claim 37, which reduces receptor-mediated or ion channel-mediated signal transduction.

83. **(Canceled)**

84. **(Original)** The adzyme of claim 37, which alters proliferation, differentiation or viability of a cell *in vivo* or *in vitro*.

85. **(Canceled)**

86. **(Currently Amended)** The adzyme of claim [[1]] 5, wherein said one or more products are ~~of said chemical reaction is an~~ antagonists of said substrate.

87. **(Withdrawn)** The adzyme of claim 1, wherein said product of said chemical reaction has an increased biological activity relative to said substrate.

88. **(Withdrawn)** The adzyme of claim 37, which alters an intrinsic enzymatic activity of said biomolecule.

89-90. **(Canceled)**

91. **(Currently Amended)** The adzyme of claim [[90]] 38, wherein said polypeptide is present in biological fluid of an animal.

92. **(Canceled)**

93. **(Original)** The adzyme of claim 91, wherein said biological fluid is blood or lymph.

94. **(Canceled)**

95. **(Currently Amended)** The adzyme of claim [[90]] 38, wherein said ~~polypeptide~~ substrate is a polypeptide hormone, a growth factor and/or a cytokine.

96. **(Canceled)**

97. **(Original)** The adzyme of claim 91, wherein said polypeptide is selected from the group consisting of four-helix bundle factors, EGF-like factors, insulin-like factors, β-trefoil factors and cysteine knot factors.

98. **(Canceled)**

99. **(Currently Amended)** The adzyme of claim 91, wherein said polypeptide is a ~~pro-inflammation~~ pro-inflammatory mediator and said enzyme construct reduces the pro-inflammatory activity of said polypeptide factor.

100. **(Canceled)**

101. **(Original)** The adzyme of claim 91, wherein said polypeptide is Interleukin-1 or TNFα, and said adzyme reduces the activity of the substrate *in vivo*.

102. **(Canceled)**

103. **(Withdrawn, Currently Amended)** The adzyme of claim [[1]] 5, wherein the substrate is an intracellular biomolecule.

104. **(Withdrawn)** The adzyme of claim 103, wherein said adzyme further comprises a transcytosis moiety that promotes transcytosis of the adzyme into the cell.

105. **(Withdrawn)** The adzyme of claim 1, wherein said targeting moiety is a polyanionic or polycatonic binding agent.

106. **(Withdrawn)** The adzyme of claim 1, wherein said targeting moiety is an oligonucleotides, a polysaccharide or a lectin

107. **(Currently Amended)** The adzyme of claim [[1]] 5, wherein the targeting domain ~~moiety~~ is an antibody or polypeptide(s) including an antigen binding site thereof.

108. **(Currently Amended)** The adzyme of claim 107, wherein the targeting domain ~~moiety~~ is selected from the group consisting of a monoclonal antibody, an Fab and $F(ab)_2$, an scFv, a heavy chain variable region and a light chain variable region.

109. **(Withdrawn, Currently Amended)** The adzyme of claim [[1]] 5, wherein said substrate is receptor ligand, and said targeting moiety includes a ligand binding domain of a cognate receptor of said ligand.

110. **(Withdrawn, Currently Amended)** The adzyme of claim [[1]] 5, wherein said targeting domain ~~moiety~~ is an artificial protein or peptide sequence engineered to bind to said substrate.

111. **(Withdrawn, Currently Amended)** The adzyme of claim [[1]] 5, wherein said substrate is a receptor, and said targeting moiety is a cognate ligand of said receptor.

112. **(Canceled)**

113. **(Currently Amended)** The adzyme of claim 101, wherein the substrate is TNFα and wherein the targeting domain ~~moiety~~ binds to TNFα.

114. **(Canceled)**

115. **(Original)** The adzyme of claim 113, wherein the catalytic domain comprises a protease that decreases TNFα pro-apoptotic activity.

116. **(Canceled)**

117. **(Original)** The adzyme of claim 115, wherein the protease is selected from among: MT1-MMP; MMP12; tryptase; MT2-MMP; elastase; MMP7; chymotrypsin; and trypsin.

118. **(Canceled)**

119. **(Original)** The adzyme of claim 113, wherein the targeting moiety is selected from among, a soluble portion of a TNFα receptor and a single chain antibody that binds to TNFα.

120. **(Canceled)**

121. **(Withdrawn, Currently Amended)** The adzyme of claim 113, wherein the targeting domain ~~moiety~~ is an sp55 portion of TNFR1.

122. **(Canceled)**

123. **(Withdrawn)** The adzyme of claim 101, wherein the substrate is IL-1 and wherein the targeting moiety binds to IL-1.

124. **(Canceled)**

125. **(Withdrawn)** The adzyme of claim 123, wherein the catalytic domain comprises a protease that decreases an IL-1 bioactivity.

126. **(Canceled)**

127. **(Currently Amended)** An adzyme preparation for therapeutic use in a human patient, the preparation comprising an adzyme of claim [[1]] 5.

128. **(Original)** The adzyme preparation of claim 127, further comprising a pharmaceutically effective carrier.

129. **(Original)** The adzyme preparation of claim 127, wherein the adzyme preparation is formulated such that autocatalytic modification of the adzyme is inhibited.

130. **(Original)** The adzyme preparation of claim 129, wherein the adzyme comprises a catalytic domain that is a protease.

131. **(Original)** The adzyme preparation of claim 130, further comprising a reversible inhibitor of said protease.

132. **(Original)** The adzyme preparation of claim 131, wherein the reversible inhibitor is safe for administration to a human patient.

133. **(Original)** The adzyme preparation of claim 127, wherein said adzyme preparation is substantially pyrogen free.

134. **(Original)** The adzyme preparation of claim 127, wherein said adzyme preparation is packaged with instructions for administration to a patient.

135. **(Withdrawn, Currently Amended)** A method of making a medicament for use in treating a disorder that is associated with an activity of the substrate of an adzyme of claim [[1]] 5, the method comprising formulating the adzyme for administration to a human patient.

136. **(Withdrawn, Currently Amended)** A method of making a medicament for use in treating an inflammatory or allergic disorder, the method comprising formulating an adzyme of claim [[1]] 5 for administration to a human patient in need thereof, wherein the substrate of the adzyme is an inflammatory cytokine.

137. **(Withdrawn, Currently Amended)** A method of treating a disorder that is associated with an activity of the substrate of an adzyme of claim [[1]] 5, the method comprising administering a therapeutically effective dose of the adzyme to a human patient in need thereof.

138. **(Withdrawn, Currently Amended)** A method of treating an inflammatory of allergic disorder, the method comprising administering a therapeutically effective dose of an adzyme of claim 5 to a human patient in need thereof, wherein the substrate of the adzyme is an inflammatory cytokine.

139-146. **(Canceled)**

147. **(Withdrawn, Currently Amended)** A method for manufacturing an adzyme, the method comprising

a) culturing a cell comprising an expression vector comprising a nucleic acid encoding the adzyme of claim 5, ~~of claim 143~~ in conditions that cause the cell to produce the adzyme ~~encoded by the expression vector~~; and

b) purifying the adzyme to substantial purity.

148. **(Withdrawn, Currently Amended)** A method for manufacturing an adzyme, the method comprising

a) culturing a cell comprising an expression vector comprising a nucleic acid encoding the adzyme of claim 25, ~~of claim 144~~ in conditions that cause the cell to produce the adzyme ~~encoded by the expression vector~~; and

b) purifying the adzyme to substantial purity.

149. **(Canceled)**

150. **(Withdrawn)** The method of claim 147, wherein the purifying the adzyme to substantial purity includes the use of a reversible inhibitor that inhibits autocatalytic activity of the catalytic domain.

151. **(Withdrawn)** The method of claim 147, wherein the catalytic domain of the adzyme is a protease domain, and wherein purifying the adzyme to substantial purity includes the use of a reversible protease inhibitor that inhibits the protease activity of the catalytic domain.

152-155. **(Canceled)**

156. **(Original, former 2nd Claim 104)** The adzyme of claim 1, wherein the targeting moiety comprises a polypeptide or polypeptide complex.